
Therapeutic Management of Preterm Newborns with Patent Ductus Arteriosus in Epiclatino Units in the Period 2015-2020.

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ABSTRACT: Introduction: In the new-born, persistent patent ductus arteriosus is associated with significant morbidity and mortality. Normally at birth, ductus arteriosus contracts causing intraluminal ischemic hypoxia that ultimately leads to closure and remodelling of the ductus. Currently, the medical management of PAD is based on the use of non-selective inhibitors of the cyclooxygenase enzyme that participates in the synthesis of prostaglandins, especially indomethacin, acetaminophen, and ibuprofen, which promote closure of the communication by up to 70% -93%. Materials and methods: Observational, retrospective, and analytical study in which records from the EpicLatino database were used. Results: 1243 patients were obtained, 52% of patients received some type of treatment and, 171 preterm patients received treatment with acetaminophen, with an increase in the trend in its use from the year 2015 to 2020. Conclusions: More treatment was used as lower the gestational age was. The use of indomethacin and ibuprofen has decreased from 2015 to 2020 due to the adverse effects they cause compared to acetaminophen.

KEYWORDS: Ductus Arteriosus, Patent; altitude; Heart Defects, Congenital; Cardiovascular Abnormalities; Neonatology.

I. INTRODUCTION

Patent ductus arteriosus (PDA) is one of the most common heart conditions. The appearance of PDA is inversely related to gestational age and weight, with a higher incidence in premature newborns [1], although in most cases it is not congenital heart disease. In the newborn, persistent patent ductus arteriosus is associated with significant morbidity and mortality. Normally, at birth, the contracting ductus arteriosus causes intraluminal ischemic hypoxia that leads to closure and remodelling of the duct [2]. PDA in term newborns is usually associated with a functional defect, probably congenital, while in preterm infants it is associated with immaturity.

Clinical signs of ductal patency include characteristic continuous heart murmur of left axillary projection, tachycardia, hyperdynamic precordium, increased systo-diastolic difference, wide peripheral pulses, signs of congestive heart failure, metabolic acidosis, difficulty in being extubated, and requirement for elevated ventilatory parameters.

Symptoms are not always present; therefore, cardiac ultrasound is the gold standard if PAD is suspected [3]. Four management strategies for PDA are currently available: fluid restriction, diuretics, pharmacologic intervention, and surgical ligation. Pharmacological closure can be achieved through the administration of drugs such as indomethacin, ibuprofen, and acetaminophen, and there are different studies regarding their efficacy and expected results, as well as the final need to require surgical ligation to resolve the condition [1, 4].

Currently, the medical management of PAD is based on non-selective inhibitors of the cyclooxygenase (COX) enzyme that participates in the synthesis of prostaglandins, especially indomethacin, and ibuprofen, which promote closure of the communication by up to 70-93%. The net effect of these drugs is to decrease prostaglandin E2 concentrations, which under physiological conditions tends to keep communication open [5, 6].

The utility of acetaminophen has also been suggested as a pharmacological alternative for PDA closure with fewer adverse effects. This would exert its action by inhibiting the peroxidase site that prevents the synthesis of prostaglandin E2. The reduction of prostaglandin levels favors constriction of the ductus arteriosus with profound hypoxia in the ductal vasa vasorum and promotes angiogenesis, intimal neof ormation, and apoptosis [7]. These characteristics, together with platelet recruitment, generate obstruction, fibrosis, and definitive closure of the ductus arteriosus. The optimal timing, doses, and benefits of medical treatment or surgical ligation have not been fully identified, so pharmacological management should be used whenever possible [8].

Therapeutic Management of Preterm Newborns with Patent Ductus Arteriosus in Epiclatino Units in the Period 2015-2020.

II. MATERIALS AND METHODS

This is an observational, retrospective, and analytical study in which the records of the database of the neonatology area of the units that make up the EpicLatino network, the Latin American database of neonatal units, were used. All newborns diagnosed with patent ductus arteriosus with a gestational age of fewer than 37 weeks between the years 2015 and 2020 were included, and those with incomplete data registration, deaths, and the presence of other congenital malformations were excluded.

Qualitative variables were analyzed using contingency tables, and association measures (Chi-square). For the other variables, a hierarchical binary risk (YES or NO treated) mixed logistic regression model was used that included altitude, years, and units (Bayesian statistics, in the Stata 17 statistical program).

III. RESULTS

In the period between 2015 and 2020 with the patients of the EpicLatino units, a sample of 8,211 premature infants under 37 weeks was obtained, of which 1,243 (15%) were diagnosed with patent ductus arteriosus, with a similar percentage diagnosed during the study period, with the highest prevalence in 2016 with 19% and the year with the lowest prevalence in 2018 with 13% (Table 1).

Table 1. Prevalence of patent ductus arteriosus in the study period 2015 - 2020. Source: Authors.

Year of diagnosis	Patients without PDA	Patients with PDA	PDA percentage	Total cases
2015	573	120	17%	693
2016	830	190	19%	1,020
2017	1,388	228	14%	1,616
2018	1,522	221	13%	1,743
2019	1,427	269	16%	1,696
2020	1,228	215	15%	1,443
Total	6,968	1,243	15%	8,211

Of the patients with a positive diagnosis of ductus (1243 premature babies), 657 (52%) patients received some type of treatment (Table 2) and figure 1 shows the logistic regression \pm CI of the risk of using a treatment for closure of the ductus. patent ductus arteriosus adjusted for gestational age (GA), altitude above sea level, year of diagnosis, and unit.

Table 2. Total number of patients with PAD who received treatment during the study period. Source: Authors.

Years	PDA no treated	PDA treated (Yes)	Percentage of treated PDA	Total cases
2015	51	69	58%	120
2016	87	103	54%	190
2017	110	118	52%	228
2018	83	138	62%	221
2019	138	131	49%	269
2020	117	98	46%	215
Total	568	657		1243

Therapeutic Management of Preterm Newborns with Patent Ductus Arteriosus in Epiclatino Units in the Period 2015-2020.

Figure 1. Logistic regression \pm CI of the risk of using a treatment for patent ductus arteriosus closure adjusted for Gestational Age (GA), altitude above sea level, year of diagnosis, and unit. **Source:** Ángela B. Hoyos, Pablo Vásquez Hoyos.

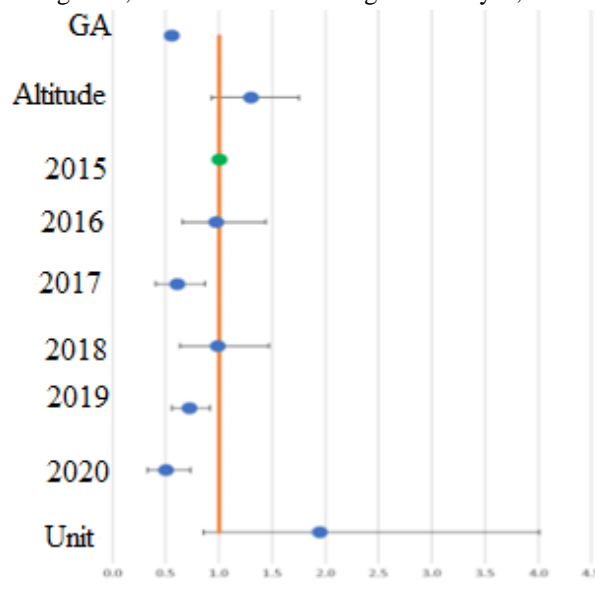
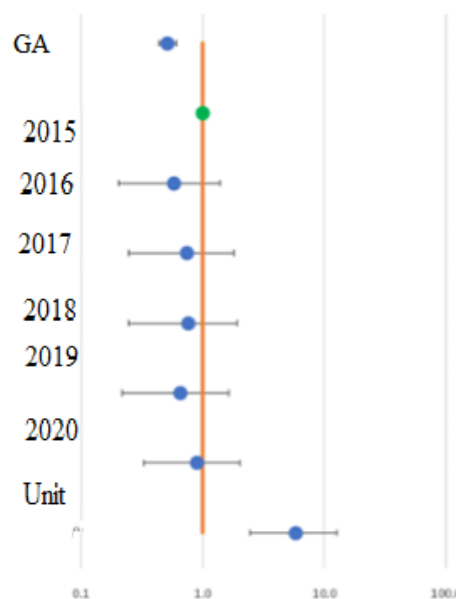


Table 3 and Figure 2 summarize the use of acetaminophen treatment.

Table 3. Use of acetaminophen to closure patent ductus arteriosus per year in preterm infants less than 37 weeks of gestation. **Source:** Authors.

Year of diagnosis	Patients with other treatments	Patients treated with acetaminophen	Percentage of patients treated with acetaminophen
2015	51	12	19%
2016	87	16	16%
2017	110	31	22%
2018	83	24	22%
2019	138	40	22%
2020	117	48	29%
Total	586	171	15%

Figure 2. Logistic regression \pm CI of the risk of using acetaminophen for closure of patent ductus arteriosus adjusted for Gestational Age (GA), height above sea level, year of diagnosis, and unit. Produced by: Ángela B. Hoyos, Pablo Vásquez-Hoyos.



Therapeutic Management of Preterm Newborns with Patent Ductus Arteriosus in Epiclatino Units in the Period 2015-2020.

Table 4. Use of ibuprofen for closure of patent ductus arteriosus per year in preterm infants less than 37 weeks of gestation. **Source:** Authors.

Year of diagnosis	Patients with other treatments	Patients treated with ibuprofen	Percentage of patients treated with ibuprofen
2015	51	25	33%
2016	87	25	22%
2017	110	31	22%
2018	83	43	34%
2019	138	29	17%
2020	117	18	13%
Total	586	171	

Figure 3. Logistic regression ± CI of the risk of ibuprofen use for closure of patent ductus arteriosus adjusted for Gestational Age (GA), height above sea level, year of diagnosis, and unit. **Source:** Ángela B. Hoyos, Pablo Vásquez Hoyos.

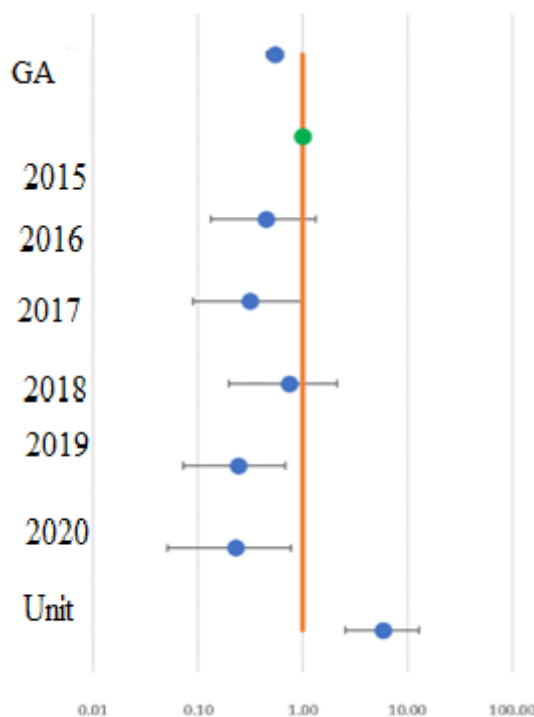


Table 5. Percentage of patent ductus arteriosus ligation in the study period in preterm infants less than 37 weeks gestation. **Source:** Authors.

Year of diagnosis	Patients with other treatments	Patients treated with ligation	Percentage of patients treated with ligation
2015	51	13	20%
2016	87	15	15%
2017	110	10	8%
2018	83	15	15%
2019	138	9	6%
2020	117	17	13%
Total	586	79	

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IV. DISCUSSION

Table 1 shows the data of patients who were diagnosed with PAD. It is important to recognize the limitations of working on a database such as EpicLatino for diagnosis since it depends on the unit (when the ECHO is done).

Therapeutic Management of Preterm Newborns with Patent Ductus Arteriosus in Epiclatino Units in the Period 2015-2020.

Among the number of patients with a positive diagnosis of ductus (1,243 premature babies), according to the data obtained, 657 (52%) patients received some kind of treatment (Table 2). It is important to highlight the treatment frequency table where a decrease in the percentage of treatment is evident from the year 2015 with 58% of the ductus treated until 2020 with 98 cases treated, which is equivalent to 46% of the total cases in the year that received treatment. In 2018, greater treatment was evidenced with 62%. According to the statistics obtained, a slightly higher prevalence is evident among the male sex with 52% to the female sex with 48%.

As can be seen in figure 1, the logistic regression of the risk factor for treating a patient with patent ductus arteriosus is related to gestational age and height does not play a significant role. Over the years, the risk of treatment has decreased since 2015 and again the units do not have a widely dispersed role.

As can be seen in figure 2 and table 2, the risk of treatment with acetaminophen, ibuprofen, or ligation, which significantly depends on gestational age, has not changed in the years compared to 2015. This treatment is dependent on the unit. Of the total number of patients receiving treatment (757 patients), 171 premature infants with PAD receive treatment with acetaminophen, and as can be seen in Table 3, an increase in the trend in its use between 2015 and 2020 of 29%. In contrast, to the statistics obtained concerning to ligation, where only 11% of the total number of patients underwent ligation, with a tendency to decrease its use over the years (Table 5).

Figure 3 and table 4 show that treatment with ibuprofen, as well as with indomethacin, has had a decrease in its use in the course of 2015 to 2022 compared to acetaminophen and is largely dependent on the unit and the gestational age.

It is important to contrast the prevalence reported in different bibliographies, such as in the randomized, double-blind, placebo-controlled, non-inferiority clinical study in Se In Sung premature infants where the prevalence is similar to 18% in the entire population [9]. In our study, a similar number is seen for the percentage of patients diagnosed during the years 2015 and 2020, which varies between 13 and 19%.

Patent ductus arteriosus in the Epic Latino units is slightly more frequent in men than in women, as mentioned in the international bibliography, without really being a widely significant value in the difference between one sex and another, in men with 52% and women with 48%.

As previously mentioned, of the 1,243 premature infants diagnosed with PAD, 52% of patients received some type of treatment. It is important to mention that at least half of the patients have received conservative management treatment, and it can also be seen that from 2015 to 2020 there are a greater tendency to use conservative management treatment, there is a treatment peak in 2018 in the increase in treatment (62%); however, we consider that it is an event related to the units and the trend of diagnosis or case reports. In the same way, it can be contrasted with the difficulty of having a database and the importance of having the moment in which treatment was started or in the same way the size of the arterial defect for which it was considered to treat or not to do so.

It is important to mention that the risk factor for starting treatment of a patient with patent ductus arteriosus is related to gestational age, height does not play a significant role. We can demonstrate this data with the same tendency as the international bibliography where the diagnosis of ductus arteriosus is greater the lower the gestational age and therefore the start of treatment. As we mentioned before, we do consider the factor of knowing the size of the defect and the age of diagnosis important to decide on the management of PAD.

As stated in the bibliography, currently, the medical management of PDA is based on non-selective inhibitors of the enzyme cyclooxygenase (COX) that participates in the synthesis of prostaglandins, especially indomethacin, and ibuprofen, which promote the closure of communication up to 70-93%; however, as it is known that the adverse effects in the medium and short term in neonates are important [10, 11, 12]. As we can see from our study the use of indomethacin and ibuprofen has decreased from 2015 to 2020, we assume this finding has to do with the adverse effects that occur in comparison with acetaminophen, which on the contrary, has a greater use from 2015 to the present..

V. CONCLUSIONS

PDA in the Epic Latino units is slightly more frequent in men than in women, as mentioned in the bibliography [4].

The appearance of PDA is inversely related to gestational age and there is more treatment the lower the gestational age. In the study period from 2015 to 2020, a decrease in the use of indomethacin and ibuprofen is observed due to the adverse effects they cause compared to the increase in the use of acetaminophen for pharmacological management. There is a trend of expectant management in recent years in EpicLatino units instead of pharmacological-surgical management, as has been seen in the current literature [5, 6].

Therapeutic Management of Preterm Newborns with Patent Ductus Arteriosus in Epiclatino Units in the Period 2015-2020.

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